Antibiotic efficacy in patients with a moderate probability of acute rhinosinusitis: a systematic review

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Abstract: The aim of this systematic review was to synthesize the results of original studies assessing antibiotic efficacy at different time points after initiating treatment in patients with a moderate probability of acute bacterial rhinosinusitis. We searched the Cochrane library for systematic reviews on the efficacy of antibiotic treatment in patients with acute rhinosinusitis (ARS). Only randomized controlled trials (RCTs) that compared treatment of any antibiotic with placebo were included. The synthesis of the results of six RCTs showed a benefit of antibiotic treatment compared to placebo for the rate of improvement after 3 [pooled odds ratio (OR) 2.78 (95 % confidence interval (CI) 1.39–5.58)] and 7 [OR 2.29 (95 % CI 1.19–4.41)] days after initiation in patients with symptoms and signs of ARS lasting for 7 or more days. After 10 days [pooled OR 1.36 (95 % CI 0.66–2.90)], improvement rates did not differ significantly between patients treated with or without antibiotics. Compared to placebo, antibiotic treatment relieves symptoms in a significantly higher proportion of patients within the first days of treatment. Reporting an overall average treatment efficacy may underestimate treatment benefits in patients with a self-limiting illness.

DOI: https://doi.org/10.1007/s00405-015-3506-z

Antibiotic efficacy in patients with a moderate probability of acute rhinosinusitis: a systematic review

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SUMMARY

Background: The aim of this systematic review was to synthesize the results of original studies assessing antibiotic efficacy at different time points after initiating treatment in patients with a moderate probability of acute bacterial rhinosinusitis.

Methodology: We searched the Cochrane library for systematic reviews on the efficacy of antibiotic treatment in patients with acute rhinosinusitis (ARS). Only randomized controlled trials (RCTs) that compared treatment of any antibiotic with placebo were included.

Results: The synthesis of the results of six RCTs showed a benefit of antibiotic treatment compared to placebo for the rate of improvement after 3 [pooled odds ratio (OR) 2.78 (95% confidence interval (CI) 1.39 to 5.58)] and 7 [OR 2.29 (95% CI 1.19 to 4.41)] days after initiation in patients with symptoms and signs of ARS lasting for 7 or more days. After 10 days [pooled OR 1.36 (95% CI 0.66 to 2.90)], improvement rates did not differ significantly between patients treated with or without antibiotics.

Conclusions: Compared to placebo, antibiotic treatment relieves symptoms in a significantly higher proportion of patients within the first days of treatment. Reporting an overall average treatment efficacy may underestimate treatment benefits in patients with a self-limiting illness.

Key words: acute rhinosinusitis, acute sinusitis, antibiotics, antimicrobial treatment, randomized controlled trial

INTRODUCTION

Antibiotics are effective in patients with acute rhinosinusitis (ARS) only in cases involving bacterial origin. Viruses cause most ARS, but discriminating between viral and bacterial rhinosinusitis is challenging and impossible in daily practice. In consequence, too many patients with ARS receive antibiotics [1-3]. Expert consensus guidelines recommend antibiotics only for patients with severe symptoms persisting for 10 days or more or for worsening of symptoms after initial improvement [4,5,1]. Authors who have synthesized the results from original studies on the efficacy of antibiotics did not address this specific patient population explicitly in their reviews, and their conclusions about the use of antibiotics in patients with ARS do not reflect agreement. One group of authors concluded that ARS resolves without antibiotic treatment [6], another group found that the overall efficacy of antibiotics is moderate [7], and a third group recommended prescribing the cheapest antibiotic [8].

The goal of systematic reviews is to support physicians and guideline developers in formulating their recommendations, but physicians sometimes have reservations about the results of these reviews, including a concern that some study results are synthesized that should not be [9]. Reasons for concern about synthesizing results from original studies include relevant differences among original studies in patient baseline characteristics or even unknown distributions of patient characteristics (e.g., duration of symptoms, fever present or not), differences in how (e.g., cure or improvement) and when (3, 10, or more days after treatment started) outcome was assessed, and inclusion of results from original studies with a moderate or even high risk of bias. A particular challenge is the synthesis of results from studies assessing treatment efficacy in patients with an illness such as ARS, for which even the presence or absence of the illness is difficult to establish.

The aim of this review was to synthesize results from a set of original studies assessing

the efficacy of antibiotics compared to placebo in patients with a presumably moderate probability of ARS based on patient symptoms and signs.

MATERIALS AND METHODS

Literature search

We searched the Cochrane library for the terms “acute rhinosinusitis”, “acute sinusitis”, “antibiotic”, and “antimicrobial” in the title, abstract, or key words to identify systematic reviews on the efficacy of antibiotic treatment in patients with ARS. From the identified reviews, only randomized controlled trials (RCTs) that compared treatment of any antibiotic with placebo were eligible for further analysis. Non-randomized trials and observational studies were excluded. Our reporting is based on the recommendations of the PRISMA statement [10].

Eligibility criteria

All RCTs included in the identified systematic reviews that met the following criterion were considered eligible: original studies that compared treatment of any antibiotic with placebo in patients with symptoms and signs of ARS lasting for 7 or more days with or without fever, i.e., a minimal duration of 7 or more days of symptoms and signs. The rationale to include only studies including patients with a duration of symptoms and signs (e.g., nasal discharge, purulent secretion, facial pain) lasting more than 7 days is based on the recommendation published in the “European Position Paper on Rhinosinusitis and Nasal Polyps” [1]. Those authors recommend antibiotic treatment only in patients with a duration of symptoms of more than 10 days. Because no original study was available that included only patients with this duration of symptoms, we modified the inclusion criteria for this review to 7 or more days. No limits for the study setting or language of the publication were applied. We excluded RCTs comparing treatment with any antibiotic versus any antibiotic.

Study selection, data extraction, and data synthesis

The bibliographic details of all retrieved original studies were stored in an Endnote file. The full texts of the RCTs were reviewed by two reviewers independently (xx and xx). Researchers with specific language proficiencies were used for non–English language references. For each RCT included in this systematic review, both reviewers independently extracted data on study design, demographic characteristics, inclusion and exclusion criteria, duration of symptoms, treatment regimens including dosage and duration, use of concomitant drugs, clinical outcomes by group including number of patients and withdrawals, and time points of measurement. When the results of one original study were included in several publications, the most recent publication was chosen for this review, and missing information was added from previous publications. Disagreements were discussed and resolved by consensus or by third-party arbitration (xx).

Outcomes

The primary outcome of this systematic review focused on cure or improvement at different days of assessment. Cure was defined as complete resolution of signs and symptoms from rhinosinusitis, and improvement was defined as a reduction of signs and symptoms. Therefore, we categorized the following outcomes as cure: “restored” [11,12] and “entirely improved” [13]. “Much better” and “somewhat better” [11,12] were categorized as improvement.

All patients who were categorized as cured are by definition improved; thus, we counted the number of improved and cured patients for the primary outcome of improvement.

Assessment of risk of bias

Two reviewers (xx and xx) independently assessed the risk of bias of all included RCTs using the Cochrane Collaboration's tool for risk-of-bias assessment [14]. Disagreements were resolved by consensus.

Adverse events

We collected data about adverse events following the addendum of the CONSORT statement for better reporting of harms in randomized trials [15].

Statistical analysis

For the statistical analysis, we used R statistical software for Windows [16] and the package 'metaphor' [17]. We classified the studies into two groups: The first group consisted of studies for which outcome was assessed at pre-specified time points (e.g., 3 days after randomization); in the second group, outcome was assessed at different days during a specific time frame (e.g., 7 to 12 days after randomization). We used a random effects model for pooling when I-squared was more than 50%.

RESULTS

Study selection

Fig. 1 summarizes the selection process for inclusion and exclusion. We identified seven systematic reviews assessing efficacy of antibiotics in patients with ARS [7,18-20,6,21,22]. In the seven systematic reviews, 21 RCTs were included comparing treatment of any antibiotic with placebo in patients with ARS. All were reviewed in full text, and six RCTs were eligible for our analysis, resulting in exclusion of 15 RCTs. Eleven of the excluded RCTs did not mention duration of symptoms in the set of inclusion criteria [23-33], two RCTs investigated rhinosinusitis only in children [34,35], the results of one RCT were not published [36], and one RCT did not report data on efficacy of antibiotic treatment compared to placebo at specified days after randomization [37].

Study characteristics

Table 1 presents the study characteristics of all RCTs included in this systematic review and meta-analysis (detailed information about inclusion/exclusion criteria and outcome definitions are summarized in Supplementary Table 1). Two RCTs compared amoxicillin [38,13], one RCT moxifloxacin (fourth-generation fluoroquinolone) [39], and one RCT azithromycin (macrolide antibiotic) [40] with placebo. Two RCTs compared two antibiotics in separated groups (penicillin V and amoxicillin) versus placebo [11,12].

The most recent RCT was conducted in 2012 [38], and the years of publication were between 1996 and 2012. Five RCTs had a double-blind design [39,40,11-13], and one RCT was triple-blinded [38].

In total, 781 patients were included in the six RCTs, and 520 (67%) were females. Sample size ranged from 63 to 169 patients, and mean patient age was 37 years. No RCT reported the number of patients with fever at baseline. In four RCTs, the authors mentioned

the presence of fever in the set of inclusion criteria [39,11,12,38]; in one RCT, authors reported that the average body temperature was 36.7°C ± 0.5 [13]; and in the remaining study, the authors did not document the presence of fever [40]. Only Hadley et al. [39] mentioned fever as a compulsory inclusion criterion. Concomitant drugs were explicitly allowed in all RCTs except for Haye et al. [40], who did not report information about concomitant drug use.

For the confirmation of bacterial origin of the ARS, only Hadley et al. [39] used sinus puncture and included only patients with positive cultures. Two RCTs took a sample either of nasal secretions [40] or from the nasopharynx [11], but verification of bacteria was not a mandatory inclusion criterion. Three RCTs did not report on sampling from the sinus or nasal secretions [38,12,13].

Risk of bias

Table 2 shows the risk of bias of all included RCTs. Four RCTs were found to have a low risk of bias [40,11-13], and one RCT was found to have an uncertain risk of bias in one of the six domains [38]. The remaining RCT was found to have an uncertain risk in four of the six domains [39].

Efficacy of antibiotics

Fig. 2 shows the odds ratios for the efficacy of antibiotics compared to placebo assessed at specific time points. Most RCTs showed a positive effect of antibiotic treatment over different observation periods (3–14 days). However, in many studies, the difference between antibiotics and placebo was not statistically significant. Lindbaek et al. (1996) [11] showed that treating patients with penicillin V or amoxicillin was significantly effective for the outcome ‘improvement’ at day 3 and for the outcome ‘cure’ at day 10. The pooled odds ratio

for improvement on day 3 was 2.78 [95% confidence interval (CI) 1.39 to 5.58]. The mean rate of improvement after 3 days was 66.4% (range 36.5% to 84.9%) in patients treated with antibiotics, and the mean rate in the placebo group was 44.4% (range 34.6% to 73.3%). In contrast, the pooled odds ratio for improvement on day 10 was 1.38 [95% CI 0.66 to 2.90]; for cure on day 10, it was 1.92 (95% CI 0.63 to 5.80). The mean rate of improvement on day 10 was 87.6% (range 77.6% to 97.7%) in patients treated with antibiotics, and the mean rate in the placebo group was 84.8% (range 80.2% to 88.6%).

Fig. 3 shows the odds ratios for the efficacy of antibiotics versus placebo assessed at different days during a specific time frame. Haye et al. [40] found a significant benefit for placebo treatment for the outcome 'cure' on days 10–12 but not on days 3–5 or 23–27. For the endpoint 'improvement', no significant differences were shown. The treatment with moxifloxacin in Hadley et al. [39] for the endpoint cure showed no significant effect. Because both studies assessed their outcomes at different time points (e.g., 3–5, 6–8, 10–12 days), we refrained from pooling the results.

Relapse/Recurrence

In Garbutt et al. [38], eight patients (9%) treated with amoxicillin had a relapse (see definition in Supplementary Table 1), and five patients (6%) treated with amoxicillin had recurrent symptoms (see definition in Supplementary Table 1). In the placebo group, five patients (6%) had a relapse, and two patients (2%) reported recurrent symptoms. In Haye et al. [40], four patients (5%) in the antibiotic group had a relapse between days 10–12 and seven patients (8%) between days 23–27. By contrast, only three patients (4%) treated with placebo had a relapse between days 10–12 and four patients (5%) between days 23–27.

Adverse events

The recording and reporting of the adverse effects are summarized in Table 3. Data about adverse events were collected by personal (n=5) or telephone (n=1) [13] interviews. None of the six studies reported using a structured questionnaire or a patient diary to collect any adverse event. The evaluations (time frame of surveillance) were carried out between days 3–27. All studies reported frequencies of adverse events, but only one study reported on severity of adverse events [11]. Between zero [13] and three patients [39] per study withdrew from the study because of an adverse event in the treatment group. The most frequent adverse events were headache, nausea/vomiting, and diarrhoea. Supplementary Table 2 shows the number of all adverse events for the treatment and placebo group per study.

DISCUSSION

The synthesis of the results of the six RCTs shows a benefit of antibiotic treatment compared to placebo in patients with ARS symptoms and clinical signs for more than 7 days. Three and seven days after the initiation of an antimicrobial treatment, the rate of improvement in patients with antibiotics was significantly higher than in controls. After 10 days, there was no significant difference in the improvement rates between patients treated with or without antibiotics. ARS, with a few exemptions, is a self-limiting illness; therefore, the only small and non-significant difference after 10 days is not entirely unexpected. The number of adverse events reported in the original studies varied widely, from 5% to over 50%. The most frequently reported adverse effects were diarrhoea and nausea/vomiting, and only a small number of patients withdrew from the studies because of adverse events of antibiotic treatment.

To our knowledge, this meta-analysis is the first to assess the outcome of improvement at specific time points (at days 3, 7, and 10). ARS is in general a self-limiting illness, and an effect of antibiotic treatment, if any, is expected after 2 to 3 days of treatment [38]. Six previous meta-analyses assessed clinical outcomes within different time frames (e.g., 3–5 days, 7–11 days) [7,18-22], and in only one were results pooled for the endpoint 'cure' – indicating patients are free of any symptoms – at specific time points [6]. In four reviews, authors concluded that antibiotics exert a small benefit [19,20,18,7] whereas other authors concluded that antibiotics have no positive effect [6,21,22].

According to a guideline [5] and a position paper [1], antibiotic treatment is recommended for patients with a duration of symptoms, including fever, of 10 or more days or worsening of symptoms after initial improvement. The results of our review support the recommendations in the guidelines that antibiotics are effective for these patients. The proportion of patients with improvement of symptoms 3 and 7 days after starting treatment

was significantly higher in the group treated with antibiotics, and there seemed to be no relevant difference in the rate of improvement or cure rate after 10 days. For clinicians, the judgment to recommend antibiotics or not to patients with suspected ARS is challenging. Although the average efficacy of antibiotics measured 10 or more days after initiation of treatment seems to be insignificant, treatment with antibiotics is an option for patients who want to have a faster improvement of symptoms.

Prevention of complications of bacterial rhinosinusitis, such as meningitis or orbital or brain abscess, is sometimes mentioned as a reason for antibiotic treatment [19]. These complications are rare but serious. In all six RCTs, patients with severe symptoms, e.g., high fever, were excluded. These patients might carry the highest risk for severe complications, and for clinicians, it may be important to know that these patients were not included in the original studies.

In further clinical trials assessing the efficacy of antibiotic treatment in patients with ARS, methodological quality could be improved in two respects: precise reporting about the presence or absence of fever and recording and reporting of adverse effects. According to the guidelines, fever should be present in patients treated with antibiotics. In the published studies, we could not analyse patients with or without fever separately and compare the efficacy of antibiotic treatment between the two groups. Furthermore, an improvement in the recording and reporting of adverse effects would be very helpful for clinicians. The efficacy of antibiotic treatment in patients with ARS, even when present, is not very large. Therefore, knowledge about the frequency, severity, and duration of adverse effects is essential for advising patients about treatment.

A strength of our study is that we pooled outcome results assessed at different, specific time points. Measurements within a time frame are more inaccurate because symptoms and signs can change quickly for illnesses such as ARS with a high rate of spontaneous

resolution. Furthermore, we included only RCTs that compared antibiotic treatment with placebo. We followed the general principle that head-to-head trials comparing the treatment effect of two or more antibiotics should be conducted when placebo-controlled trials have shown that treatment is better than placebo [41].

The main limitation of this study is the small number of RCTs available that compared antibiotic treatment with placebo in patients with ARS. Furthermore, inclusion criteria and definitions of outcomes as well as their assessment varied among the included RCTs.

Our meta-analysis shows that antibiotic treatment compared to placebo relieves symptoms in a significantly higher proportion of ARS patients within the first days of treatment. However, the potential for adverse effects must be considered. In addition, in terms of the method of synthesizing results from original studies, reporting an overall average treatment efficacy in patients with an illness that has a high probability of spontaneous cure may underestimate treatment benefits.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Fig. 1 Study flow

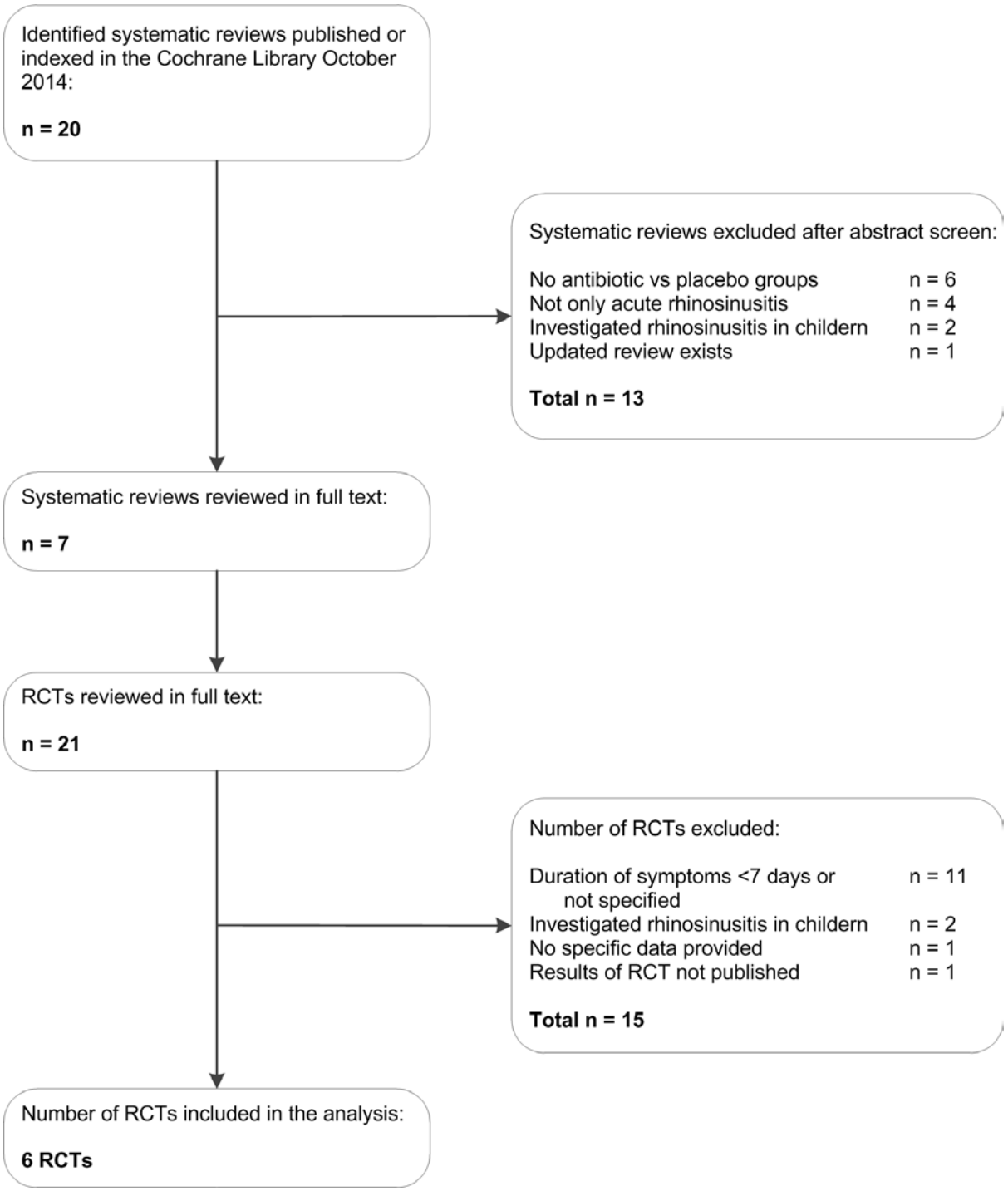

Fig. 2 Efficacy of antibiotics assessed at specific time points

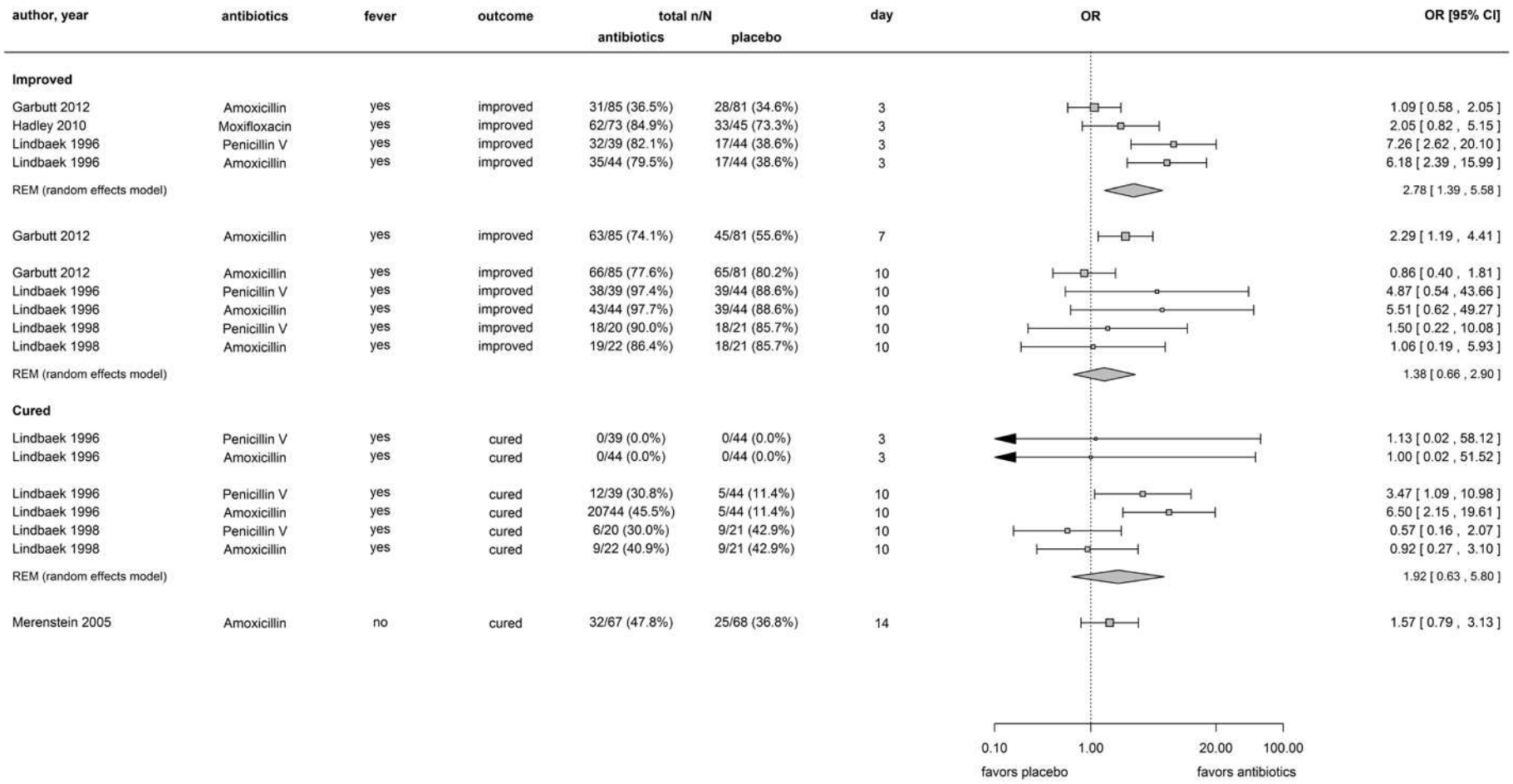

Fig. 3 Efficacy of antibiotics assessed at different days during a specific time frame

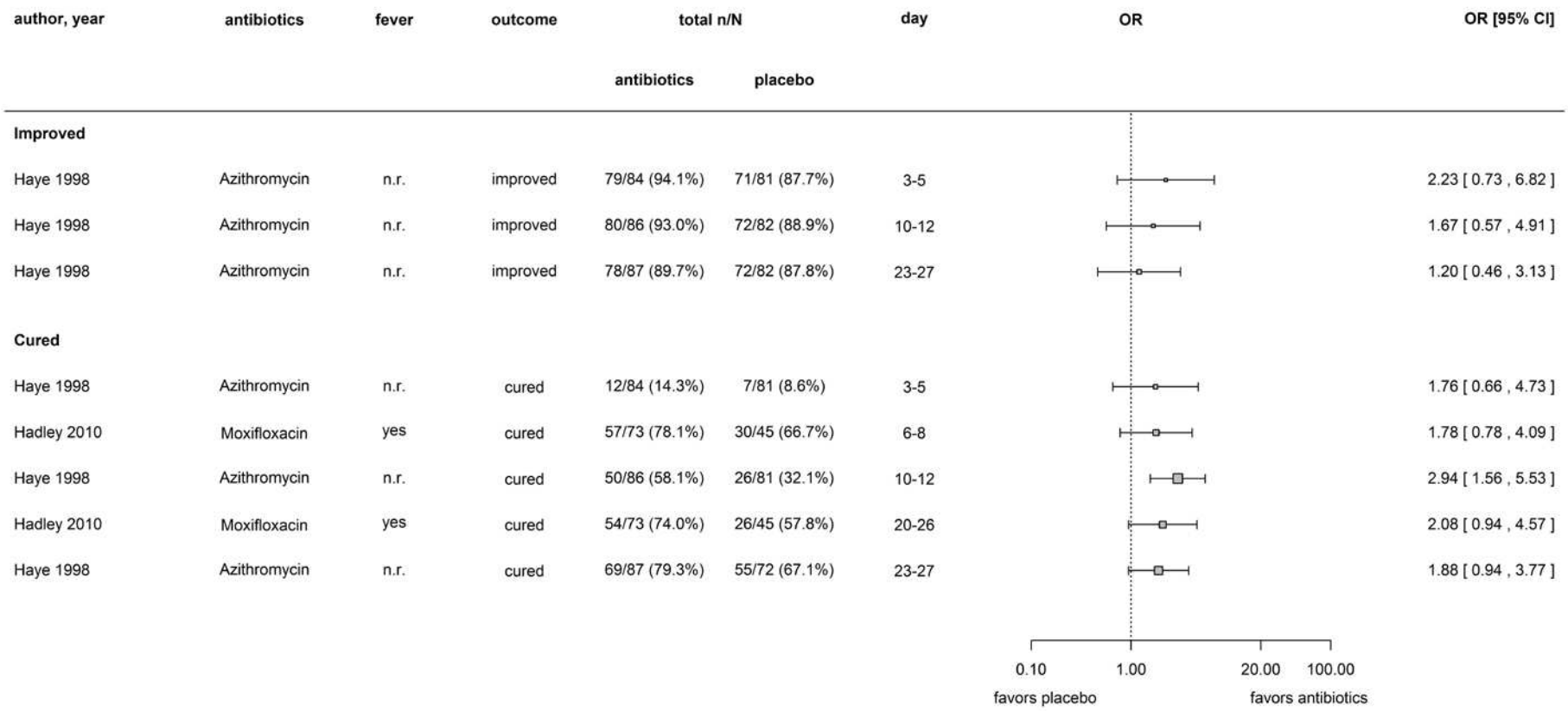

Table 1: Baseline characteristics of the six included RCTs

Author, year	Number of patients (women)	Age mean: years (SD or range)	Duration of symptoms: days (SD)	Concomitant drugs allowed	Intervention	Control intervention	Outcome classification
Garbutt, 2012 [38]	166 (106)	31.5 (18-69)	7-28 (11.1)	yes	Amoxicillin 500mg 3x daily for 10 days	Placebo	significant improvement, relapse, recurrence
Hadley, 2010 [39]	118 (73)	38.5 (13.4)	7-27 (12.7)	yes	Moxifloxacin 400mg 1x daily for 5 days	Placebo	cure, improvement
Haye, 1998 [40]	169 (125)	41.7 (18-70)	11-29 (n.r.)	n.r.	Azithromycin 500mg 1x daily for 3 days	Placebo	cure, improvement, failure, relapse
Lindbaek, 1996 [11]	130 (85)	38.6 (16-74)	8-29 (n.r.)	yes	Group 1: Penicillin V 1320mg Group 2: Amoxicillin 500mg 3x daily for 10 days	Placebo Placebo	restored, much better, somewhat better, unimproved, worse
Lindbaek, 1998 [12]	63 (38)	40.2 (15.9)	8-29 (n.r.)	yes	Group 1: Penicillin V 1320mg Group 2: Amoxicillin 500mg 3x daily for 10 days	Placebo Placebo	restored, much better, somewhat better, unimproved, worse
Merenstein, 2005 [13]	135 (93)	33.8 (9.8)	≥7 (11.2)	yes	Amoxicillin 500mg 3x daily for 10 days	Placebo	improved, not improved

n.r. not reported

Table 2: Risk-of-bias assessment of all included RCTs

Author, year	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective outcome reporting?	Free of other bias?
Garbutt, 2012 [38]	+	+	+	?	+	+
Hadley, 2010 [39]	?	?	?	+	+	?
Haye, 1998 [40]	+	+	+	+	+	+
Lindbaek, 1996 [11]	+	+	+	+	+	+
Lindbaek, 1998 [12]	+	+	+	+	+	+
Merenstein, 2005 [13]	+	+	+	+	+	+

+ low risk, *?* uncertain risk, - high risk

Table 3: Recording and reporting of adverse events

Author, year	Drug therapy	Number of patients with AEs n (%)	Number of patients with treatment related AEs n (%)	Number of patients with AEs in placebo group n (%)	Withdrawal because of AEs (due to harm) n	Seriousness or Severity of AEs	Evaluation of attribution: event related to antibiotic	Data collection by personal interview	Data collection by telephone interview	Data collection by structured questionnaire	Data collection by patient diary	Timeframe of surveillance (at day)
Garbutt, 2012 [38]	Amoxicillin	14/85 (16)	not specified	11/81 (14)	1	n.r.	n.r.	yes	no	n.r.	n.r.	10
Hadley, 2010 [39]	Moxifloxacin	96/251 (38.2)	34/251 (13.5)	50/123 (40.7)	3	n.r.	yes	yes	no	n.r.	n.r.	3-4, 6-8, 14-18
Haye, 1998 [40]	Azithromycin	n.r.	24/87 (27.6)	15/82 (18.3)	0	n.r.	yes	yes	no	n.r.	n.r.	3-5, 10-12, 23-27
Lindbaek, 1996 [11]	Penicillin V	24/41 (58.5)	not specified	16/44 (36.4)	2	reported	n.r.	yes	no	n.r.	n.r.	3, 10
Lindbaek, 1996 [11]	Amoxicillin	25/45 (55.6)	not specified	16/44 (36.4)	1	reported	n.r.	yes	no	n.r.	n.r.	3, 10
Lindbaek, 1998 [12]	Penicillin V	1 (5)*	not specified	n.r.	1	n.r.	n.r.	yes	no	n.r.	n.r.	10
Lindbaek, 1998 [12]	Amoxicillin	2 (9,1)*	not specified	n.r.	2	n.r.	n.r.	yes	no	n.r.	n.r.	10
Merenstein, 2005 [13]	Amoxicillin	13/57 (22.8)	not specified	7/59 (11.9)	0	n.r.	n.r.	no	yes	n.r.	n.r.	3, 7, 14

Table 4: Reporting of adverse events

Author, year	Drug therapy	Number of patients with AEs n (%)	Number of patients with treatment related AEs n (%)	Number of patients with AEs in placebo group n (%)	Withdrawal because of AEs (due to harm) n	Seriousness or Severity of AEs	Evaluation of attribution: event related to antibiotic
Garbutt, 2012 [38]	Amoxicillin	14/85 (16)	not specified	11/81 (14)	1	n.r.	n.r.
Hadley, 2010 [39]	Moxifloxacin	96/251 (38.2)	34/251 (13.5)	50/123 (40.7)	3	n.r.	yes
Haye, 1998 [40]	Azithromycin	n.r.	24/87 (27.6)	15/82 (18.3)	0	n.r.	yes
Lindbaek, 1996 [11]	Penicillin V	24/41 (58.5)	not specified	16/44 (36.4)	2	reported	n.r.
Lindbaek, 1996 [11]	Amoxicillin	25/45 (55.6)	not specified	16/44 (36.4)	1	reported	n.r.
Lindbaek, 1998 [12]	Penicillin V	1 (5)*	not specified	n.r.	1	n.r.	n.r.
Lindbaek, 1998 [12]	Amoxicillin	2 (9,1)*	not specified	n.r.	2	n.r.	n.r.
Merenstein, 2005 [13]	Amoxicillin	13/57 (22.8)	not specified	7/59 (11.9)	0	n.r.	n.r.

n.r. not reported, *AE* adverse event, * Only gastrointestinal AEs were reported

Supplementary Table 1: Inclusion and exclusion criteria, outcome definitions as reported in the original studies

Author, year	Study setting	Inclusion criteria	Exclusion criteria	Outcome definitions
Garbutt, 2012 [38]	10 offices of primary care physicians, between November 1, 2006 and May 1, 2009, St. Louis, Missouri, USA	Adult patients aged 18 to 70 years who met the Centers for Disease Control and Prevention's expert panel's diagnostic criteria for acute bacterial rhinosinusitis were assessed, if their symptoms were moderate, severe, or very severe. Diagnosis required history of maxillary pain or tenderness in the face or teeth, purulent nasal secretions, and rhinosinusitis symptoms for 7 days or more and 28 days or less that were not improving or worsening, or rhinosinusitis symptoms lasting for less than 7 days that had significantly worsened after initial improvement.	Patients were excluded if they had an allergy to penicillin or amoxicillin, prior antibiotic treatment within 4 weeks, complications of sinusitis, a comorbidity that may impair their immune response, cystic fibrosis, required an antibiotic for a concurrent condition, were pregnant, or rated their symptoms as very mild or mild.	*significant improvement:* self-rating: symptoms a lot better or absent (no symptoms) *relapse:* at day 10 significantly improved, but on day 28 symptoms unchanged or worse *recurrence:* at days 7 and 10 no symptoms, and at day 28 symptoms worse
Hadley, 2010 [39]	37 centers (ear, nose, and throat practices; family practitioners; and general medical clinics), USA	Patients were eligible for inclusion if they were ≥18 years of age and had a clinical diagnosis of ABRS with signs and symptoms present for ≥7 days but <28 days as defined by radiographic and clinical criteria. Radiographic criteria included the presence of air-fluid levels and/or opacification on a radiographic paranasal sinus film (Waters' view). Eligible patients also had two major symptoms (purulent anterior or posterior nasal discharge and unilateral facial pain or malar tenderness), or at least one major and one minor symptom (frontal headache or fever [oral >38.0°C, tympanic >38.5°C, axillary ≥37.5°C]) as defined by the Sinus and Allergy Health Partnership.	History of chronic sinusitis, defined as >4 weeks of continuous symptoms; sinus surgery <6 months previously; symptoms that suggest the patient's current illness is allergic rhinitis, known bacteremia, meningitis, or infection spreading beyond the sinuses; known immunodeficiency disease; receipt of systemic antibacterial therapy likely to be effective in the treatment of ABRS for >24 hours within 7 days of enrollment; requirement for concomitant systemic corticosteroids or systemic antibacterial therapy with agents other than those specified in the protocol; current receipt of topical nasal corticosteroids, unless the patient had been on a stable dose for >4 weeks prior to enrollment; pregnancy or breast-feeding; receipt of an investigational	*cure:* resolution or improvement in the signs and symptoms such that no further therapy (antimicrobial, corticosteroid or irrigation) was required *improvement:* improvement in the patient's signs and symptoms, and continuation of therapy

			drug in the past 30 days; and a history of allergy to quinolone antimicrobials or related compounds	
Haye, 1998 [40]	General Practices, Norway	Patients of either sex aged 18 to 70 years with a history of an upper respiratory tract infection and with clinical symptoms and signs indicative of but without radiological evidence of acute maxillary sinusitis were recruited and computer-randomized in blocks of six to either of the two treatment groups. The diagnosis was based on the physicians' clinical findings, which had to include one or both of the following symptoms: presence of nasal secretion (purulent at the time of examination) for >10 and <30 days, and maxillary sinus tenderness and/or pain of <30 days' duration. To exclude the presence of empyema, plain radiographs using Waters' projection (occipitomental view) could not show complete opacity or an air-fluid level, and the mucosal thickness must be < 6 mm as measured at the upper lateral border of the maxillary sinus. In addition, radiographs using Caldwell projection (occipitofrontal) were performed to exclude frontal sinusitis and lateral projection to exclude sphenoidal sinusitis.	Women who were pregnant or breast feeding or of child bearing potential but not using appropriate contraception, patients with a history of intolerance to macrolides, azalides, penicillin, or lactose, patients with more than two prior episodes of sinusitis during the last 12 months, patients who had taken antibiotics within the preceding 2 weeks, those having extensive caries and/or periodontal disease, concurrent acute infections, or those using ergotamine.	*cure:* disappearance of all pretreatment symptoms relevant to infection *improvement:* partial disappearance of pretreatment signs and symptoms *failure:* no change or a worsening of pretreatment symptoms *relapse:* initial improvement or disappearance of pretreatment symptoms followed by worsening
Lindbaek, 1996 [11]	General practices, between January and May 1994 and between November 1994 and May 1995, Tønsberg region in southern Norway	All patients were examined by one experienced general practitioner according to a standardised clinical procedure on the same day as the computed tomography was performed. The clinical signs and symptoms evaluated were scored according to being present or not or to severity. The symptoms and signs registered are all common in acute sinusitis. The presence of either hyposmia or anosmia, symptoms lasting longer than seven days before the first visit, unilateral facial	Age 15 and under, pregnancy, ongoing antibiotic treatment, immunosuppressive treatment, previous operations in the nose or sinus region, misuse of alcohol or narcotics, rheumatic disease, and allergy to penicillin, symptoms persisted for more than 30 days (due to a possible chronic sinusitis), patients with high fever and strong pain (because of ethical consideration)	self-rating (restored, much better, somewhat better, unimproved, worse) without a more specific definition of these terms

		pain, pain in upper teeth, pain worsening on bending forward, or two phases in the disease history each scored one point. Nasal obstruction, rhinorrhoea, sinus pain, and malaise estimated by the patient gave a maximum of one point each. Rectal temperature between 37.6 and 38.0°C scored 0.5 and above 38.0°C one point. Purulent secretion in the nasal floor, which is a fairly consistent sign of purulent sinusitis, was given two points. The points were summated for each patient, resulting in a "clinical severity score" of a maximum of 13 points. A bacteriological sample from the nasopharynx was taken at the time of the clinical examinations.		
Lindbaek, 1998 [12]	General practices, between January and May 1994 and between November 1994 and May 1995, Tønsberg region in southern Norway	Included were patients who were clinically diagnosed as having acute sinusitis, and had mucosal thickening without fluid levels or total opacification upon CT examination. All patients were examined by an experienced family physician according to a standardized clinical procedure, the same day as the CT was performed. The clinical signs and symptoms evaluated were scored according to being present or not, or to severity. The symptoms and signs registered are all common in acute sinusitis. The presence of either hyposmia or anosmia, duration of symptoms more than seven days prior to first visit, unilateral facial pain, pain in upper teeth, pain worsening at bending forward, and double sickening (two phases in the same illness period) prior to first visit, each scored one point. Nasal obstruction, rhinorrhoea, sinus pain, and malaise as estimated by the patient, gave a maximum of one point each. Rectal temperature between 37.6°C and	Age of 15 years or younger, pregnancy, ongoing antibiotic treatment, immuno-suppressive treatment, previous operations in the nose/sinus region, abuse of alcohol or narcotics, rheumatic disease, and penicillin allergy. If the symptoms had persisted more than 30 days, the patient was excluded due to a possible chronic sinusitis. Patients with high fever and considerable pain (due to ethical considerations)	self-rating (restored, much better, somewhat better, unimproved, worse) without a more specific definition of these terms

		38.0°C scored 0.5 points and above 38.0°C 1 point. Purulent secretion in the nasal floor, which is a fairly consistent sign of purulent sinusitis, was given 2 points. The points were summated for each patient, resulting in a "clinical severity score" of maximum 13 points.		
Merenstein, 2005 [13]	Suburban primary care office, between October 1, 2001 and March 31, 2003, USA	Patients were eligible to participate if they were 18 years or older; had at least 1 cardinal feature described by the clinical prediction rule: 1) purulent nasal discharge predominating on one side, 2) local facial pain predominating on one side, 3) purulent nasal discharge on both sides, or 4) pus in the nasal cavity; and had symptoms for at least 7 days.	antibiotic treatment within the past month, allergy to penicillin, sinus surgery, compromised immunity, pneumonia, or streptococcal pharyngitis	self-rating (entirely improved, not improved) without a more specific definition of these terms

Supplementary Table 2: Frequency of reported adverse events by group

Author, year	Garbutt, 2012 [38]		Hadley, 2010 [39]		Haye, 1998 [40]		Lindbaek, 1996 [11]			Lindbaek, 1998 [12]			Merenstein, 2005 [13]	
Type of AE	**Amoxicillin n (%)**	**Placebo n (%)**	**Moxifloxacin n (%)**	**Placebo n (%)**	**Azithromycin n (%)**	**Placebo n (%)**	**Penicillin V n (%)**	**Amoxicillin n (%)**	**Placebo n (%)**	**Penicillin V n (%)**	**Amoxicillin n (%)**	**Placebo n (%)**	**Amoxicillin n (%)**	**Placebo n (%)**
Abdominal pain	4 (5)*	n.r.			3 (3.4)	1 (1.2)							2 (3.5)	1 (1.7)
Diarrhea	8 (9)*	n.r.	5 (2)	2 (1.6)	11 (12.6)	5 (6.1)	15 (37)	21 (47)	5 (11)				4 (7)	1 (1.7)
Dizziness			6 (2.4)	0 (0)									3 (5.3)	0 (0)
Dry mouth													1 (1.8)	0 (0)
Excessive tiredness	9 (11)	17 (21)												
Gastrointestinal side-effects										1 (5)	2 (9.1)	n.r.		
Headache/asthenia	19 (22)	19 (23)					4 (10)	5 (11)	6 (14)					
Hot flashes													0 (0)	1 (1.7)
Jittery													0 (0)	1 (1.7)
Nausea/vomiting	6 (7)*	n.r.			7 (8)	1 (1.2)	10 (24)	14 (31)	5 (11)				5 (8.8)	5 (8.5)
Rash							0 (0)	5 (11)	2 (5)				2 (3.5)	0 (0)
Vaginal discharge							0 (0)	5 (11)	1 (2)					
Vaginal infection	5 (6)*	n.r.											2 (3.5)	0 (0)

n.r. not reported, *AE* adverse event, * Reported numbers mentioning that there were no differences between study groups